PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 32918/PC/MDE	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/SI 03/00043	International filing date *(day/month/year)* 25.11.2003	Priority date *(day/month/year)* 26.11.2002
International Patent Classification (IPC) or both national classification and IPC A61K9/16		
Applicant LEK PHARMACEUTICALS D.D. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.06.2004	02.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Hedegaard, A Telephone No. +49 89 2399-8644

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/SI 03/00043

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-15 as originally filed

Claims, Numbers

1-18 received on 15.02.2005 with letter of 15.02.2005

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

   see separate sheet

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-18
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item I

Basis of the report

1. An essential feature, namely "obtained by wet granulation" has been omitted from the newly filed claims 1 and 16; contrary to the provisions of Article 34(2)(b) PCT.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

   D1: EP-A-0080862
   D2: EP-A-1025841
   D3: WO-A-9733564
   D4: WO-A-03063820
   D5: WO-A-95 25516 (mentioned in the application)

   If not indicated otherwise, the relevant passages are those mentioned in the International Search Report.

   D1 discloses formed particles comprising amoxicillin and clavulanic acid, said particles obtained by wet granulation using an organic solvent (e.g. acetone or dichloromethane) and binder. The granular mass is extruded and dried.

   D2 discloses tablets comprising amoxicillin and potassium clavulanate obtained by non-aqueous wet granulation with a binder, drying, sieving and optionally coating.

   D3 discloses moist granulation of amoxycillin trihydrate and potassium clavulanate with water-free organic solvents. Furthermore, D3 discloses the production of agglomerates of amoxicillin using solvents such as acetone.

D5 (see claims 1, 3 and 5) discloses granules comprising amoxycillin and/or potassium clavulanate and one or more surfactants (such as sodium lauryl sulphate). The granules are obtained by wet granulation and spheronization (see D5, p. 3, l. 3-16).

2. The subject-matter of claim 1 is not novel (Art. 33(2) PCT) over D5 (see above under item 1). It is here pointed out that the surfactants according to D5 can be characterised as absorption enhancers for amoxycillin. Furthermore, nondistinctive characteristics of a particular intended use (e.g. use as absorption enhancer or spheronizing agent) are to be disregarded when examining novelty of a composition.

3. The same applies mutatis mutandis to independent claims 12, 16 and 17.

4. Should the above-mentioned novelty-objection be overcome the question of inventive step (Art. 33(3) PCT) arises. In this respect the attention is drawn to D1-D3 and D5 which discloses wet granulation of e.g. combinations of potassium clavulanate and amoxycillin (see above under item 1). The addition of an absorption enhancer is well known in the art and comes within the scope of the customary practice followed by persons skilled in the art, especially as the advantages thus achieved can readily be foreseen. Therefore, it appears that the subject-matter of present application does not involve an inventive step.

5. A positive international preliminary report for the subject-matter of the dependent claims can only be established when they refer to independent claims which meet the requirements of the PCT.

6. Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*

WO-A-03 063820	07.08.2003	31.01.2003	01.02.2002 06.02.2002

Although WO-A-03 063820 (D4) does not constitute prior art within the meaning of Rule 64.1(b) PCT, it could become of relevance in the regional phase.
No check has been made as to whether the priorities have been validly claimed.

Enclosure of February 15, 2004
International Patent Application PCT/SI03/00043
Lek pharmaceuticals d.d.

Amended Claims

1. Formed particles comprising amoxicillin and clavulanic acid and an absorption enhancer for amoxycillin.

2. The particles according to Claim 1, wherein amoxicillin is present in the form of amoxicillin trihydrate and clavulanic acid is present in the form of potassium clavulanate.

3. The particles according to Claim 1, wherein the ratio of amoxicillin to clavulanic acid is from 1:1 to 30:1.

4. The particles according to Claims 1 and 3, wherein the ratio of amoxicillin to clavulanic acid is 4:1, 7:1, 8:1, 12:1, 16:1, 20:1.

5. The particles according to claim 1, wherein the absorption enhancer is selected from the group consisting of sodium deoxycholate, sodium taurocholate, polisorbate 80, sodium lauryl sulfate, sodium dodecylsulfate, octanoic acid, sodium docusate, sodium laurate, glyceride monolaurate, stearic acid, palmitinic acid, palmitooleinic acid, glycerilmonooleate, sodium taurocholate, ethylenediaminetetraacetic acid, sodium edentate, sodium citrate, β-cyclodextrine and sodium salicylate.

6. The particles according to claim 1, wherein the absorption enhancer is selected from sodium deoxycholate, sodium docusate and sodium lauryl sulfate.

7. The particles according to Claim 1, further comprising excipients selected from fillers, binders, disintegrants, glidants, lubricants.

8. The particles of Claim 1, prepared by wet granulation using acetone.

9. The particles according to Claim 1, prepared by wet granulation using a binder dispersion in an organic solvent.

10. The formed particles according to claim 1 and 9, wherein the binder is hydroxypropyl cellulose and/or polyvinylpyrrolidone.

11. The particles according to Claim 1, which are coated or uncoated.

12. A pharmaceutical composition comprising the particles according to Claim 1.

13. The pharmaceutical composition according to Claim 12 in the form of a multiple unit formulation.

14. The pharmaceutical composition according to Claim 12 in the form of a tablet, capsule or sachet.

15. The pharmaceutical composition according to Claim 12, which is coated.

16. A Pharmaceutical composition comprising amoxycillin and clavulanic and an absorption enhancer for amoxycillin.

17. A process for the preparation of the particles according to Claim 1 comprising the following steps:

- preparation of the mixture of amoxicillin trihydrate and potassium clavulanate, absorption enhancer and excipients (with or without a binder),
- wet granulation with an organic solvent or wet granulation with a binder dispersion in an organic solvent,
- extrusion of a wet mixture through a screen,

- spheronization,
- drying of particles,
- optionally application of a coating

18. The process according to claim 19 wherein the organic solvent is acetone.